



CASE REPORT

A case of cutaneous clear cell sarcoma determined by clinicopathological and cytogenetic analysis

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ARTICLE INFO

Article history:

Received: Jul 11, 2011

Revised: Sep 5, 2011

Accepted: Nov 16, 2011

Keywords:

clear cell/diagnosis

malignant

melanoma

melanoma/diagnosis

positron emission tomography

sarcoma

ABSTRACT

Cutaneous clear cell sarcoma (CCS) is a rare soft tissue malignancy that typically manifests in the distal extremities of young adults. Although it shows melanocytic differentiation, CCS is clearly pathologically and genetically distinct from malignant melanoma. Here, we report the case of a 43-year-old male who had an asymptomatic, deep-seated, slowly enlarging, firm mass over the right heel for 30 years that recently and rapidly progressed with tenderness. We arranged for the total excision of the tumor. Pathological and cytogenetic analysis of the biopsied specimen showed that it was a clear cell sarcoma. Computed tomography and positron emission tomography scans showed no signs of metastasis, and no other abnormal hypermetabolic lesions were detected. Wide excision with split-thickness skin graft and a sentinel lymph node biopsy were performed. Because of positive findings in the sentinel lymph nodes, the patient was transferred to the plastic surgery department for further radical popliteal and inguinal lymph node dissection. The patient has received regular outpatient follow-up care in our hospital for the past 8 months with no evidence of recurrence.

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Introduction

Cutaneous clear cell sarcoma (CCS), also known as CCS of the tendons or aponeuroses or melanoma of the soft tissues, was first described in 1965 by Franz Enzinger.¹ This rare malignant neoplasm accounts for only 1% of soft tissue sarcomas.^{2–4} Clinically, most cases of CCS occur in adolescents and young adults. It typically arises in the deep soft tissues of the extremities, particularly the feet and hands, although cases have also been documented in the penis, trunk, head, and neck.^{5–9} The growth pattern is indolent in the early stages but aggressive in the late stages. The histopathological and immunohistochemical similarities between clear cell sarcoma and malignant melanoma may lead to misdiagnosis.^{5,10} Further examination using conventional chromosome analysis, fluorescent *in situ* hybridization (FISH), or reverse transcriptase-polymerase chain reaction (RT-PCR) may aid in its diagnosis.¹¹ Only one case of primary clear cell sarcoma with epidermal involvement has been reported in the literature.¹⁰ Here, we present a case of clear cell sarcoma on the right heel with skin invasion due to prolonged duration.

Case report

A 43-year-old male without a significant medical history or any traumatic injuries visited the outpatient clinic of the dermatology department of our hospital because of a palpable firm mass on the right heel that had been present for more than 30 years. The patient recalled that a bean-sized nodule had been present since childhood. The nodule was firm, unmovable, and had enlarged over the past 10 years. The lesion was biopsied 5 months prior at another hospital; the pathology report showed hyperkeratotic tissue accompanied by inflammatory cells. The biopsy wound did not heal well, so several traditional medical treatments were tried but all were unsuccessful. Thus, the patient came to us for further evaluation and management. Upon inspection, the tumor was 45 mm × 30 mm with a linear biopsy scar in the center. There was no erythema or melanin pigmentation. However, a yellowish-brown discharge with tenderness and pain over the sole were noted (Figure 1).

Under the tentative diagnosis of a hyperkeratotic or fibrous tumor with nonhealing postbiopsy wound, the patient underwent total excision of the tumor with split-thickness skin grafting. Pathological examination of the biopsied specimen revealed individual to clustered, atypical, clear, melanocytic-like tumor cells that involved the whole dermis and subcutis and projected deep into the fascial-tendon soft tissues, approaching the junctional region

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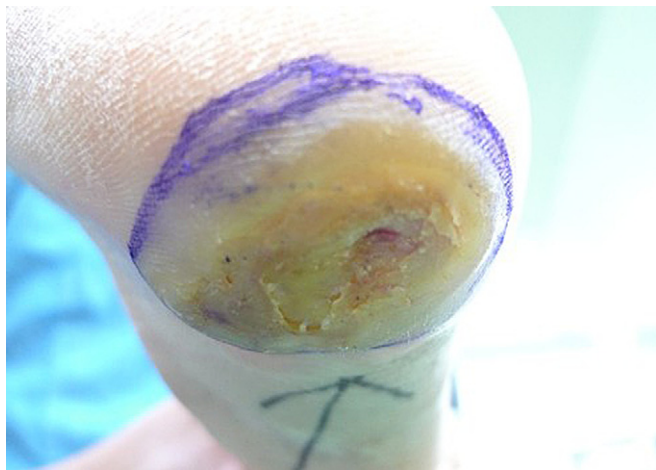


Figure 1 On the right heel, one egg-sized (4.5 × 3.0 cm), firm, subcutaneous nodule with a nonhealing ulceration surface and overlying thick hyperkeratosis. No other skin lesions were found. No obvious melanin pigmentation was noted.

and papillary dermis. The overlying epidermis showed marked reactive hyperkeratosis and focal parakeratosis, indistinct melanin pigment deposition, and no obvious pagetoid spreading (Figure 2). The tumor cells showed positive cytoplasmic staining for HMB-45 and S-100 proteins. Two tentative diagnoses were considered: cutaneous melanoma with deep soft tissue invasion or clear cell sarcoma with upward skin invasion (Figure 3).

A secondary, wider tumor excision was performed with popliteal and inguinal sentinel lymph node biopsy, which showed

positive lymph node involvement. The primary tumor location showed no residual lesions, and the calcaneal tuberosity of the bone was free of any indications of metastasis. Computed tomography and positron emission tomography scans showed no signs of metastasis or other abnormal hypermetabolic lesions. Because a positive sentinel lymph node was found, the patient was transferred to the plastic surgery department for further radical popliteal and inguinal lymph node dissection.

To confirm the diagnosis, a FISH cytogenetic study was performed. DNA *in situ* hybridization for 22q12 using the Vysis EWS gene dual-color kit (Abbott Molecular, Des Plaines, IL, USA) showed scattered break points at the 22q122 (EWS) gene (Figure 4). Therefore, clear cell sarcoma was diagnosed. The patient has made regular outpatient follow-up visits to our hospital during the 8 months after diagnosis and treatment without evidence of recurrence.

Discussion

In the case of CCS with epidermal involvement, differential diagnosis from cutaneous malignant melanoma may be difficult.¹¹ However, the distinct clinical presentation (e.g., slow and indolent growth in the early stages, very long prebiopsy duration, deep-seated location, young age, and firm consistency) and cytogenetic tests may help to arriving at the correct diagnosis.

In our case, the histological findings showed focal and upward skin involvement. However, we believe that the tumor growth started deep within the site rather than as a primary cutaneous melanoma due to hyperkeratosis and the nonerosive surface. Because the tumor grows slowly from deep within the site, the overlying epidermis become hyperkeratotic under chronic stimulation,

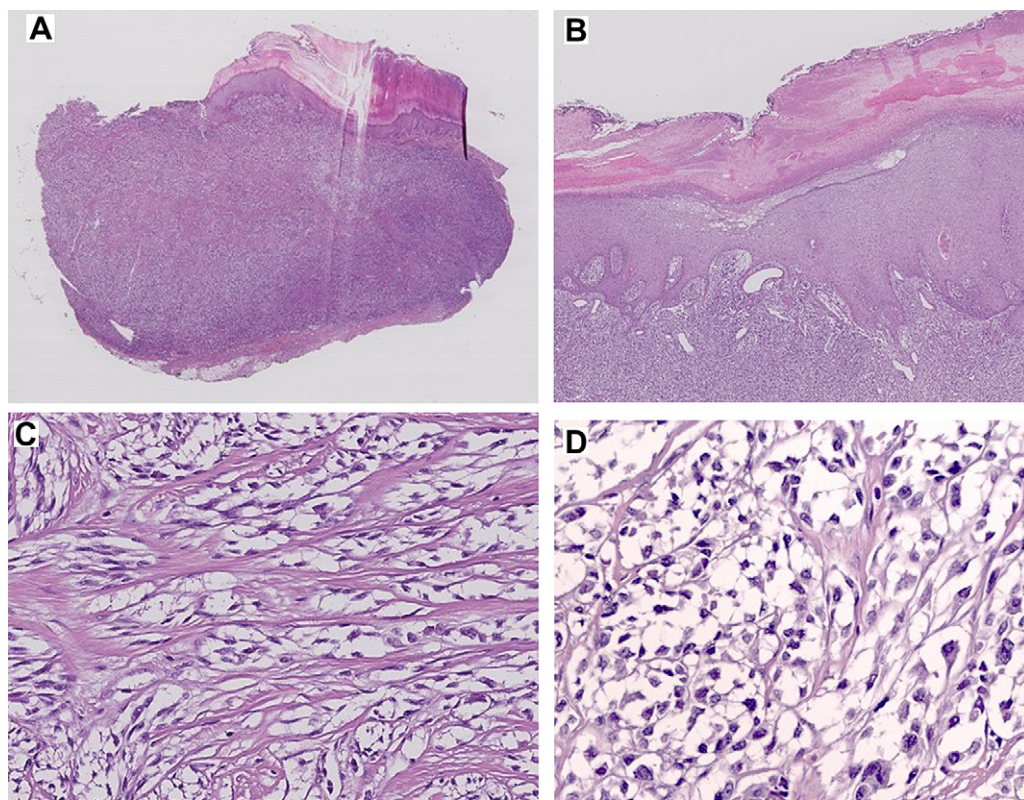


Figure 2 Microscopic analysis of the biopsied tumor cells. (A) Tumor cell nests involving the whole dermis, subcutis, and the deep fascial-tendon soft tissue (hematoxylin & eosin staining [H&E] 5×). (B) Individual to clustered atypical clear melanocytic-like tumor cells in the junctional region and papillary dermis with overlying marked reactive hyperkeratosis (H&E, 100×). (C) The tumor consists of nests of clear cells separated by irregular fibrous bundles (H&E, 200×). (D) Tumor cells with abundant clear cytoplasm and centrally located nuclei with prominent nucleoli (H&E, 400×).

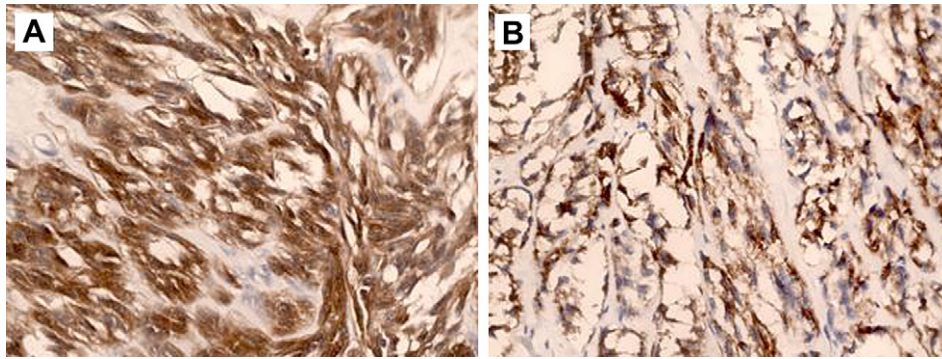


Figure 3 Immunohistochemical analysis of biopsied tumor cells showing (A) positive cytoplasmic staining for the S-100 protein (H&E, 200×) and (B) positive cytoplasmic staining for HMB-45 (H&E, 200×).

a mechanism similar to corn formation. Had the tumor grown from the junctional area, the epidermal surface would have become erosive, as commonly seen in nodular melanoma.

Histologically, CCS is highly infiltrative with haphazard arrangement into compact nests and fascicles of pale fusiform or epithelioid cells surrounded by a fine fibrous framework of tendons, fascia, and aponeuroses.^{2,11,12} The stroma may be barely visible, fibrotic, or hyalinized. The neoplastic cells of CCS are polygonal to fusiform with lightly eosinophilic cytoplasm and centrally located round-to-ovoid vesicular nuclei with prominent basophilic nucleoli. Cellular polymorphisms and mitotic figures are uncommon. The frequent appearance of multinucleated giant cells may provide a valuable diagnostic clue.¹¹

Immunohistochemically, CCS shares an identical profile with malignant melanoma and expresses S-100, HMB-45, Melan-A, and vimentin, with or without microphthalmia transcription factor.^{2,6,11,13} A recent study by Hisaoka et al showed strong S100 protein expression in 100% of cases, and expression of HMB-45, Melan-A, and microphthalmia transcription factor in 97%, 71% and 81% of cases, respectively.¹⁴

The pathological differential diagnosis of CCS includes malignant melanoma, malignant peripheral nerve sheath tumor (MPNST), and synovial sarcoma. The predominantly deep-seated location and

deep soft tissue involvement in CCS with upward tumor invasion, mostly without direct connection to the epidermis, may distinguish it from malignant melanoma. However, focal epidermal invasion, as documented in one study,¹⁰ was also observed in our patient perhaps due to long duration or the palmoplantar location. The critical distinction between CCS and malignant melanoma depends on the results of cytogenetic studies: the chromosomal translocation t(12;22)(q13;q12) and *EWSR1/ATF1* gene rearrangement, which is considered pathognomonic of CCS, is found in 75% of all cases using FISH or RT-PCR.^{2,10} MPNST is usually associated with the nerve trunk or manifests in the settings of neurofibromatosis type I, thereby revealing myxoid stroma, hyperchromatic nuclei, brisk mitotic activity, and negative staining for HMB-45 and Melan-A. Synovial sarcoma is often composed of spindle cell and glandular components that form a characteristic biphasic pattern. Besides, negative staining for HMB-45, characteristic chromosomal translocation t(X;18)(p11.2;q11.2), and *SYT/SSX1* or *SYT/SSX2* gene fusion transcripts may distinguish synovial sarcoma from CCS.

The main treatment for CCS is immediate wide excision with adequate safety margins. Chemotherapy and radiotherapy have not been shown to provide any additional benefit to the survival rate.^{2,6,15} Poor prognostic factors include tumor size (≥ 5 cm), necrosis, metastasis, and local recurrence.^{5,10,16,17} The most

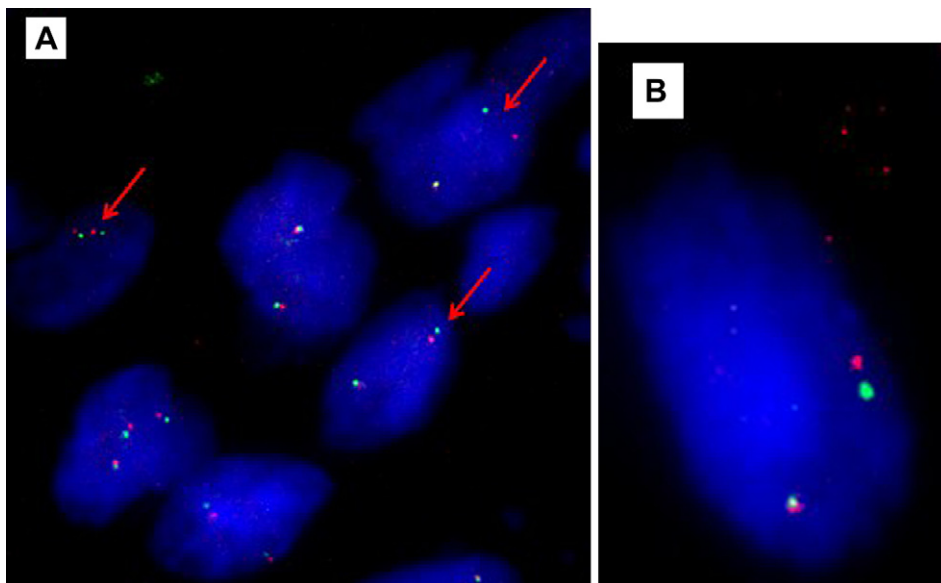


Figure 4 Detection of EWS rearrangement by fluorescence *in situ* hybridization (FISH) analysis. (A) In this case, the Vysis EWS gene dual-color kit revealed scattered break points (red arrow) in the 22q12 (EWS) gene. (B) High-power view. The split, single, red, and green signals correspond to the rearranged EWS allele.

common metastatic sites include the lymph nodes, lungs, liver, heart, brain, bone, and skin.^{5,12,18} Sentinel lymph node biopsy can detect early occult regional metastasis. The 5-year survival rate after radical resection and chemotherapy or radiotherapy has been estimated to be about 67%, while the 10-year survival rate is about 33%.^{2,3,6}

Early recognition and initial radical surgery are key factors that determine a favorable outcome, while chemotherapy and radiotherapy do not help. As shown in this case, CCS should be listed in the differential diagnosis when the histopathological features are similar to cutaneous melanoma in the lower extremities of young adults, but the tumor often takes a more indolent clinical course.

References

1. Enzinger FM. Clear-cell sarcoma of tendons and aponeuroses. An analysis of 21 cases. *Cancer* 1965;**18**:1163–74.
2. García de Marcos JA, del Castillo-Pardo de Vera JL, Poblet E, et al. Clear cell sarcoma of the temporal region: case report, review of the literature, and genetic analysis. *J Oral Maxillofac Surg* 2009;**67**:910–4.
3. Kazakos CJ, Galanis VG, Giatromanolaki A, et al. Clear cell sarcoma of the scapula. A case report and review of the literature. *World J Surg Oncol* 2006;**4**:48.
4. Van Akkooi AC, Verhoef C, Van Geel AN, Kliffen M, Eggermont AM, de Wilt JH. Sentinel node biopsy for clear cell sarcoma. *Eur J Surg Oncol* 2006;**32**:996–9.
5. Zhang W, Shen Y, Wan R, Zhu Y. Primary clear cell sarcoma of the sacrum: a case report. *Skeletal Radiol* 2011;**40**:633–9.
6. Choi JH, Gu MJ, Kim MJ, et al. Primary clear cell sarcoma of bone. *Skeletal Radiol* 2003;**32**:598–602.
7. Suehara Y, Yazawa Y, Hitachi K, Terakado A. Clear cell sarcoma arising from the chest wall: a case report. *J Orthop Sci* 2004;**9**:171–4.
8. Rubin BP, Fletcher JA, Renshaw AA. Clear cell sarcoma of soft parts: report of a case primary in the kidney with cytogenetic confirmation. *Am J Surg Pathol* 1999;**23**:589–94.
9. Saw D, Tse CH, Chan J, Watt CY, Ng CS, Poon YF. Clear cell sarcoma of the penis. *Hum Pathol* 1986;**17**:423–5.
10. Rodríguez-Martín M, Sáez-Rodríguez M, Esquivel B, González RS, Cabrera AN, Herrera AM. Clear cell sarcoma: a case mimicking primary cutaneous malignant melanoma. *Indian J Dermatol* 2009;**54**:168–72.
11. Hantschke M, Mentzel T, Rütten A, et al. Cutaneous clear cell sarcoma: a clinicopathologic, immunohistochemical, and molecular analysis of 12 cases emphasizing its distinction from dermal melanoma. *Am J Surg Pathol* 2010;**34**:216–22.
12. Dim DC, Cooley LD, Miranda RN. Clear cell sarcoma of tendons and aponeuroses: a review. *Arch Pathol Lab Med* 2007;**131**:152–6.
13. Panagopoulos I, Mertens F, Isaksson M, Mandahl N. Absence of mutations of the BRAF gene in malignant melanoma of soft parts (clear cell sarcoma of tendons and aponeuroses). *Cancer Genet Cytogenet* 2005;**156**:74–6.
14. Hisaoka M, Ishida T, Kuo TT, et al. Clear cell sarcoma of soft tissue: a clinicopathologic, immunohistochemical, and molecular analysis of 33 cases. *Am J Surg Pathol* 2008;**32**:452–60.
15. Jones RL, Constantinidou A, Thway K, et al. Chemotherapy in clear cell sarcoma. *Med Oncol* 2010;**28**:859–63.
16. Dewan M, Malatani TS, Ansari MA. Lessons to be learned: a case study approach. *Malignant melanoma of soft tissue. J R Soc Promot Health* 2005;**125**:42–6.
17. Deenik W, Mooi W, Rutgers E, Johannes P, Hart A, Kroon B. Clear cell sarcoma (malignant melanoma) of soft parts: a clinicopathological study of 30 cases. *Cancer* 1999;**86**:969–75.
18. Sciort R, Speleman F. Clear cell sarcoma of soft tissue. In: Fletcher CD, Unni KK, Mertens F, editors. *Pathology and genetics: tumours of soft tissue and bone*. Lyon: IARC Press; 2002. p. 211–2.